HYPOTHALAMIC-PITUITARY SYNDROMES*

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THE hypothalamus is a central station in the autonomic nervous system for the control and regulation of vegetative functions. By its manifold activities the hypothalamus helps to maintain a constant internal environment. The conception of a constant internal environment we owe largely to the genius of Claude Bernard. The functional role of the hypothalamus in preserving the equilibrium has been well summed up by J. Barcroft,[1] who states "The physiology of the hypothalamus is the physiology of the internal environment."

The constancy of the internal environment depends upon a multitude of chemical and physical processes, such as secretions and excretions and their underlying metabolic requirements. Since metabolism is closely connected with endocrine secretion, regulation of vegetative functions must have a nervous as well as endocrinal character. It behooves us to understand the mechanism of this nervous and glandular coöperation.

The hormones, the powerful agents of the endocrine system, act in a definite order. This plan is carried out through the hypothalamic control of their production and release from the respective glands. The hypothalamus also plays a part in determining the degree of response to these hormones on the part of tissues and organs. The best known example of this type of hypothalamic control is the resistance to insulin in a diabetes originating from a hypothalamic lesion.

The hypothalamus responds to a large number of stimuli, such as temperature, osmotic pressure, pH; and is itself influenced by hormones. According to H. H. Meyer,[2] for example, the chief action of thyroxin is exerted upon the hypothalamus. In all probability the retarding influence of a number of endocrine glands upon the anterior pituitary is mediated by the hypothalamus.

The hypothalamus lies below the level of the thalamus, in the lateral wall and in the floor of the third ventricle from the posterior border

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of the optic chiasm dorsal, including the mammillary bodies. The posterior lobe of the pituitary may be considered a part of the hypothalamus; it develops from the floor of the third ventricle and as an avantguard brings the ectodermal anterior lobe into close contact with the hypothalamus. Thus anatomy and development indicate an intimate functional relationship between the hypothalamus and the pituitary.

The posterior pituitary lobe and the tuberal region of the hypothalamus (*Zwischenhirndruese*) are the sources of various hormones. Whether they are produced within the pituicytes which represent modified ganglion cells, or in the epithelial sheaths covering the posterior lobe and the tuber cinereum, is a matter under discussion.

The pituitary-hypothalamic complex is responsible for a large number of symptoms, syndromes, and well-defined disease entities. Since the secretion of the anterior lobe rests under the command of the hypothalamus, it is practically impossible to determine which function or lesion is purely hypothalamic or purely pituitary in origin. The following table shows the chief functions depending upon hypothalamic-pituitary activity:

TABLE I

FUNCTIONS DEPENDING UPON HYPOTHALAMIC-PITUITARY ACTIVITY

General metabolism
Carbohydrate metabolism
Fat metabolism and distribution of fat
Water metabolism (renal activity, sweating)
Thirst
Hunger and appetite
Growth and trophisms
Sexual development, maturation and activity
Cardiovascular activity (cardiac rhythm, blood pressure, vasomotor balance, circulating blood volume)
Gastrointestinal activity (secretions, tonus, peristalsis)
Formation of erythrocytes, leukocytes, thrombocytes and plasma proteins
Regulation of body temperature
Sleep (hypothalamic only)

In order to avoid false deductions, it must be borne in mind that in this part of the central nervous system the anatomical localization of a lesion does not necessarily mean localization of a function (H. Jackson,[3] Lhermitte[4]). The nuclear masses in the hypothalamus do not always represent well-defined centers by which isolated functions are controlled.

TABLE II

DISORDERS OF HYPOTHALAMIC-PITUITARY ORIGIN

High BMR	Low BMR	
Diabetes mellitus	Hypoglycemia	
Diabetes renalis		
Adiposity	Wasting (Cachexia)	
Lipodystrophy		
Fever	Hypothermia	Poikilothermia
Polyuria	Oliguria	
Diabetes insipidus		
Gigantism	Dwarfism	
Insomnia	Somnolence	
Pubertas precox	Delay and regression of sex development	
Arterial hypertension	Arterial hypotension	Vasomotor instability
Excessive salivation	Diminished salivation	
Gastric superacidity	Gastric subacidity	
	Achylia gastrica	
	Gastric-duodenal ulcers	
	Anomalies of gastrointestinal tonicity	
Polycythemia	Anemia	
Leukocytosis	Agranulocytosis	
Eosinophilia		
Osteoporosis	Eburnation	
	Arthritis	
Hirsutism	Alopecia	

The many pathological features enumerated in Table II may be grouped together into syndromes or well-defined diseases.

This rather imposing list is characterized by the large number of plus-minus variations, thus affirming the regulatory capacity of the hypothalamus.

The hypothalamus constitutes an essential instrument for emotional expression, normally restrained by cortical control. When in hypothalamic disorders cortical control is weakened or lost, emotional instability and abnormal behavior come to the fore. Emotional hypothalamic attacks are certainly more frequent than corresponds with the instances reported in the literature.

Hypothalamic-pituitary syndromes are brought on by four chief causes: Inherited or congenital defects, inflammation, trauma, and tumor.

Heredity plays an important role in the production of diabetes insipidus and of Froehlich's syndrome, the dystrophia adiposogenitalis. Encephalitis caused not only by influenza but all infectious diseases, and

also vaccination are of great etiological importance. Trauma and also surgical injury have been reported to be the cause in a number of cases. Leukemic infiltrations, Boeck's sarcoid, lymphogranulomatosis and xanthomatosis as well as primary or metastatic tumors produce the syndromes either by direct destruction of the tissues of the hypothalamo-pituitary territory or by pressure exercised directly or by an internal hydrocephalus.

The allotted time will not permit consideration of all the hypothalamic-pituitary syndromes. However, by discussing a few of them, namely, diabetes insipidus, abnormal ratio of growth with infantilism (infantile gigantism), and Froehlich's syndrome we may gain a general understanding of the underlying mechanism and of the possibilities of therapy. We may start with diabetes insipidus.

Diabetes Insipidus

Diabetes insipidus originates from a disorder in the anterior hypothalamus and is controllable by the pituitary antidiuretic hormone, which is found and probably produced not only in the posterior lobe but also in the tuberal region of the hypothalamus. Therefore, total hypophysectomy need not eradicate the hormone and does not produce diabetes insipidus. Two factors underlie the genesis of diabetes insipidus, namely, absence of the antidiuretic hormone or failure of response to this hormone. Thus diabetes insipidus may exist in spite of a perfectly normal pituitary gland. It is generally agreed that physiologically the antidiuretic hormone acts on the hypothalamus itself. Of course, there is no doubt that experimentally and therapeutically the hormone is able to produce oliguria by direct action on the kidney proper and on capillaries generally. This universal action does not contravert anatomical, experimental and therapeutic evidence as to the direct influence of the antidiuretic hormone on the hypothalamus.

The nerve elements responsible for the control of the diuresis are well known. The paraventricular and supraoptic nuclei in the anterior hypothalamus are linked to the posterior lobe by the supraoptico-hypophyseal tract, abundant fibers of which take up a direct contact with the specific cells in the pars tuberalis and media. Another fiber tract runs between the tuberal nuclei and the posterior pituitary. These nuclei and the posterior lobe represent a functional unit. Destruction of the nuclei is followed by atrophy of the posterior lobe and destruc-

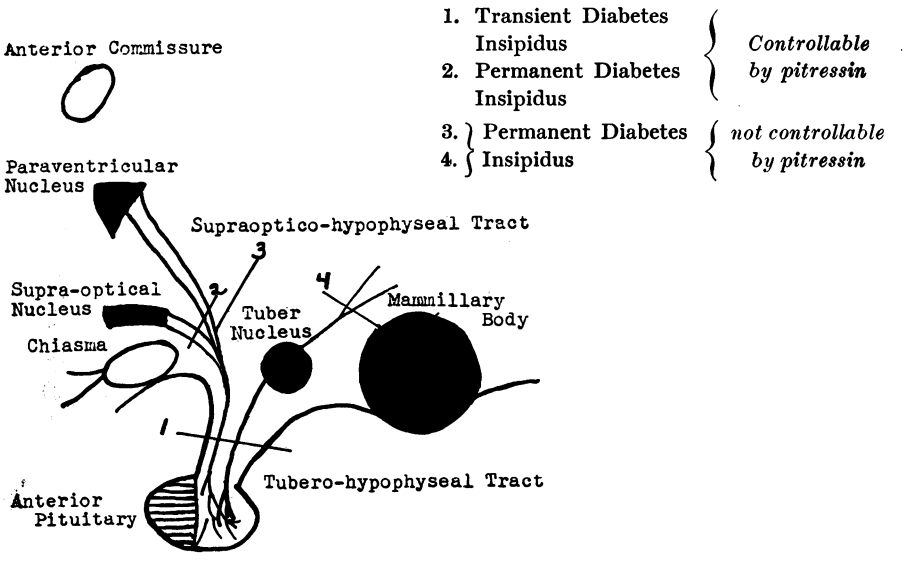

Fig. 1—The pituitary-hypothalamic control of diuresis.

tion or removal of the posterior lobe leads to atrophy of the cells of the nuclei. The destruction of the supraoptico-hypophyseal tract causes degeneration of the hypothalamic nuclei as well as of the posterior pituitary (Fisher, Ingram and Ransom[5]). Bilateral lesions within this system cause diabetes insipidus.

The investigations of Labbé and Azérad,[6] Dreyfus[7] and Biggart[8] indicate that the tuberal nuclei and the nerve tract running from these nuclei toward the mammillary bodies (tractus tuberalis descendens) possess a special importance in that lesions involving this tract render the diabetes insipidus refractory to the antidiuretic hormone.

The functional significance of diabetes insipidus lies in the fact that one of the most important renal functions is disturbed, namely, the ability of the kidney to retain water. In diabetes insipidus the excretory renal requirements cannot be fulfilled by means of a normal or small quantity of water. It is now well established that the extreme thirst of diabetes insipidus is not primary but that it is secondary to the uncontrolled diuresis.

Three types of diabetes insipidus may be differentiated. The first does not show any other symptom than polyuria. In these cases during a period of oliguria, easily enforced by the injection of the antidiuretic

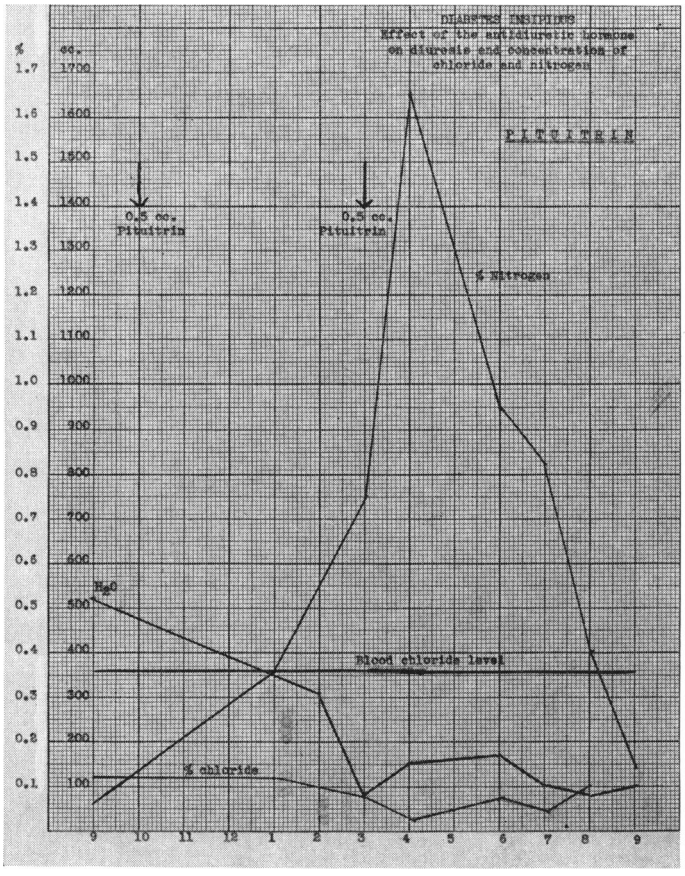

CHART I—DIABETES INSIPIDUS. Effect of the antidiuretic hormone on diuresis and concentration of chloride and nitrogen.

hormone, the kidneys reveal normal concentrating capacity. A second group is characterized by polyuria and failure in concentrating ability in respect to chlorides, bicarbonates and basic elements. Even in extreme oliguria the urinary concentration of chlorides remains unaltered—it may be as low as 100 mg. per 100 cc.—or at best it rises to the blood chloride level. Finally, there is a third type in which the polyuria decreases to inconspicuous figures, e.g., 2000 cc., but the failure to concentrate remains. This points to a hypothalamic apparatus of the concentrating power of the kidneys and its independence from the diuresis of water.

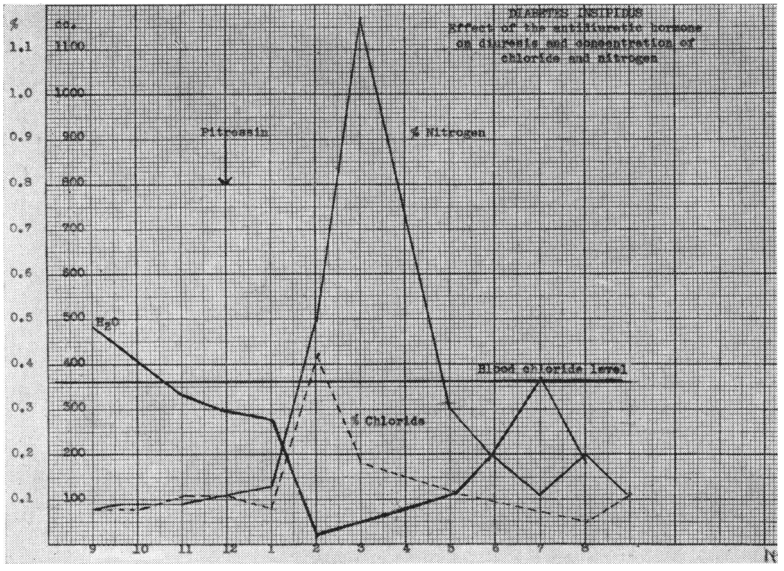

CHART II—DIABETES INSIPIDUS. Effect of the antidiuretic hormone on diuresis and concentration of chloride and nitrogen.

Diabetes insipidus may be a permanent or sporadic state, or may vary in degree, or may cease completely, just as is the case in diabetes mellitus of hypothalamic origin. In fact, even when caused by a most substantial pathological lesion, such as a metastatic cancer or a leukemic infiltration, the abnormality may disappear. This fact corresponds with experimental observations, according to which destruction of the posterior lobe or dissection of the pituitary stalk causes an increased secretory activity of the tuberal part of the hypothalamus and, therefore, a polyuria which lasts very briefly. The failure of the concentrating capacity also may be transitory in character.

Hann[9] has advocated the idea that diabetes insipidus does not develop in the absence of the anterior pituitary, which, he believes, produces a diuretic hormone. There is no satisfactory proof of the validity of this conception. However, it seems likely that inactivity of the thyroid gland, which necessarily follows the absence of thyreotropic hormone, may prevent or counteract the polyuria. Thus after total hypophysectomy diabetes insipidus can be provoked by the administration of thyroid extract. According to a case report by L. Strauss,[10] diabetes insipidus

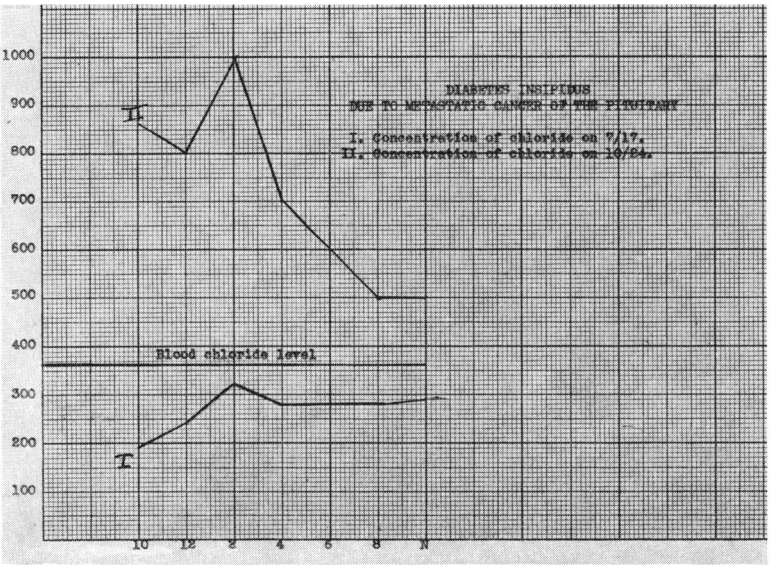

CHART III—DIABETES INSIPIDUS. Due to metastatic cancer of the pituitary. I, Concentration of chloride on 7/17. II, Concentration of chloride on 10/84.

disappeared after the development of myxedema, and T. Findley, Jr.[11] has found an increase of the effect of pitressin after thyroidectomy. These observations have led to an attempt to control diabetes insipidus by thyroidectomy. Good results have been reported in a few cases.

The functional character of diabetes insipidus is evidenced by the disappearance of the polyuria during fever, sleep, and anesthesia—conditions which temporarily change the activity of the hypothalamus.

It is well known that during sleep all the secretory and excretory processes are depressed. When this coöperation between the mechanism responsible for sleep and the control for secretory and excretory processes fails, nocturia, nocturnal salivation, night sweats and nocturnal gastrosuccorrhea result.

Etiologically we may differentiate as a separate group the idiopathic diabetes insipidus, which is frequently hereditary. In the famous family investigated by Adolf Weil,[12] of Heidelberg, and Alfred Weil,[13] of New York, 35 of 220 members in five generations suffered from the disease which in this instance happened to be a dominant hereditary character. There seem to be no records of anatomical studies on the

hypothalamus and the pituitary in idiopathic diabetes insipidus. However, even though structural alterations should not be detectable, the frequent coincidence of diabetes insipidus with other hypothalamic disorders points to the hypothalamic origin.

In the majority of the cases polyuria is the only manifestation of the hypothalamic disorder and may last throughout life, the span of which is not shortened. After the age of fifty the disturbance frequently becomes less troublesome. Pregnancy has a definite influence, either decreasing or increasing the polyuria. Rest is beneficial. The prognosis does not depend on the degree of the polyuria, even when so excessive as 43 liters a day, as in a case reported by Trousseau.

Non-idiopathic diabetes insipidus is chiefly secondary to tumors and inflammatory pathology. Particularly in children infectious diseases, such as measles, scarlet fever, pertussis, diphtheria, chickenpox, mumps, erysipelas, influenza, and also vaccination may bring on a persistent diabetes insipidus. Xanthomatosis causes diabetes insipidus in 60 per cent and pellagra in 25 per cent of the patients.

The therapy may be considered from the viewpoint of the ways and means of influencing the hypothalamus generally. This principle may be exemplified on the basis of methods which influence heat regulation and at the same time water elimination.

The Viennese school of E. P. Pick[14] has established the antidiuretic effect of antipyretics. Particularly aminopyrine has been used successfully in diabetes insipidus and has been seen to interfere with mercury diuretics. We have used aminopyrine against nocturia in cases of chronic mesencephalitis with good results, as shown in Table III.

It has been observed that in diabetes insipidus the polyuria may become diminished or even disappear during a period of fever. Fever induced by foreign proteins, or other substances, may have the same effect. Here the rise in the temperature originates in that part of the temperature center which controls the production of heat. The rise of temperature brought on by hot baths, the fever machine, or other means, is quite different in its mechanism, for here the apparatus designed to get rid of heat becomes active. The diuresis may be diminished by either mechanism or by both.

The chief agent for the treatment of diabetes insipidus is the antidiuretic hormone. It is available as the extract of the posterior and of the intermediary pituitary. Pitressin applied subcutaneously may produce

TABLE III

EFFECT OF AMINOPYRINE ON NOCTURIA

CASE	TOTAL URINE CC.	REDUCTION OF THE DIURESIS [PER CENT]	URINE DAY	URINE NIGHT	NOCTURIA IN PERCENTAGE OF TOTAL	AMINOPYRINE
I	2570		770	1800	70	
	1720	33	1070	650	30	+ +
II	2130		530	1600	75	
	1495	30	845	650	43	+ +
III	2360		860	1500	63	
	1050	56	870	180	17	+ +

oliguria for a period of 4 to 6 hours but sometimes for 24 or even 48 hours. In a small number of cases thirst is a hypothalamic symptom independent from the polyuria and not influenced by the antidiuretic hormone. In such cases treatment with antidiuretic hormone is contraindicated because the patient, continuing to take in large quantities of fluid, but unable to excrete corresponding amounts of urine, may become dangerously ill from a syndrome which has been termed "water intoxication." In another group of cases the vasomotor effect of the posterior lobe extract may cause considerable discomfort. In that event an extract of the intermediary lobe may be tried. In 1922, H. L. Blumgart[15] introduced the intranasal application of the antidiuretic hormone. This method is more effective and certainly more convenient than the subcutaneous route, provided the patient's snuffing technique is good and he can stand it without getting nasal catarrh. The nasal application of 50 mgms. of the extract is sufficient in most cases. The smallest effectual dose should be established and administered as frequently or as rarely as necessary.

According to reports in the literature, follicular hormone has been helpful in a number of cases. This effect is creditable since we know that this hormone and others counteract the activity of the anterior lobe acting via the hypothalamus. In diabetes insipidus it seems essential to depress the anterior lobe and consequently the use of anterior pituitary hormones and particularly of the thyreotropic hormone is contraindicated. This also applies to the thyroid hormone because of its diuretic

effect. An attempt may be made to depress the thyroid secretion by administering diiodotyrosine. The use of sedatives is to be recommended and may be combined with atropine and aminopyrine, particularly in cases resistant to the antidiuretic hormone. Antisyphilitic treatment will be successful in suitable cases. Removal of 8 to 15 cc. of spinal fluid by spinal puncture is recommended by Herrick and may be of value particularly in cases with increased intraventricular pressure.

Dystrophia Adiposogenitalis

Dystrophia adiposogenitalis, Froehlich's syndrome, is another pituitary-hypothalamic syndrome of major importance. It is characterized by obesity and failure or delay of sexual development. There is in New York City a particularly large number of individuals of this type, who show a strong hereditary and familial trend. Groups of human beings—I purposely avoid the misinterpreted and criminally applied term race—in which there is a tendency to obesity, as for instance in the peoples originating from Southern and Southeastern Europe and Asia Minor, seem to produce a relatively larger number of individuals of the Froehlich type.

It should be borne in mind that height and weight are stigmata of pituitary-hypothalamic origin and that the change in height which has taken place in the last twenty-five years, points to an evolutionary change in pituitary-hypothalamic activity. This last period has produced a larger number of tall individuals with long limbs and a relatively short torso, on which is perched a small head with a long face. The disproportionate growth of the limbs is caused by the delay in sex maturation. This type of abnormal ratio of growth with infantilism (infantile gigantism) represents a pituitary-hypothalamic anomaly linked to the eunuchoid type. Its somatic characteristics are paralleled by a definite mental pattern. These individuals are emotional rather than rational and are governed by sentiment rather than by reason. They have little stability, lack self-confidence and dread to assume responsibility or to face the world alone. Hence they are easily herded by a man who claims to be their leader, holding out to them prospects of green pastures and greatness. It is interesting that in the present Germany this infantile gigantism is portrayed as the ideal of manhood and knighthood in the statue of "Siegfried." (Fig. 2)

Dystrophia adiposogenitalis is usually congenital. The endocrine

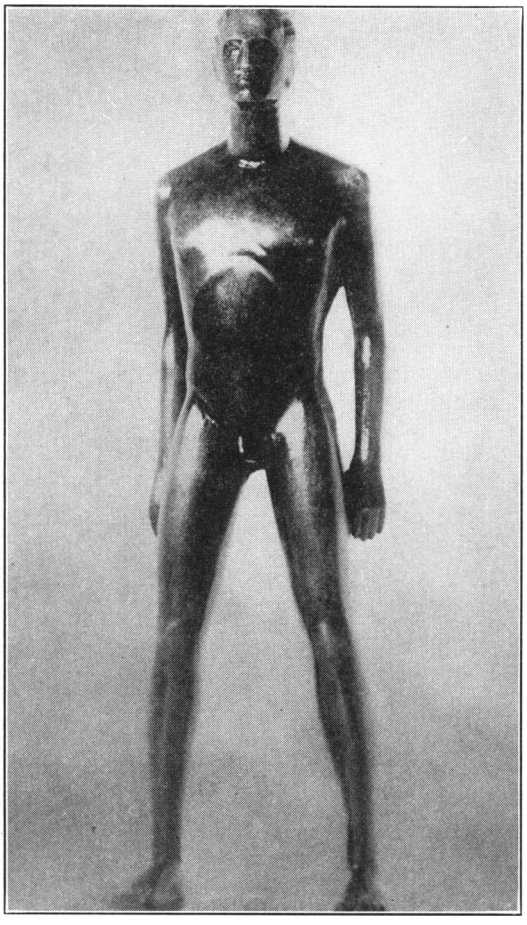

Fig. 2—"Siegfried" statue in present day Germany shows the characteristics of infantile gigantism.

and nervous origin of the outstanding symptoms—adiposity and sexual retardation—have been clarified in recent years. According to P. E. Smith,[16] destruction of the anterior pituitary causes atrophy of the gonads but not adiposity. Obesity results from basophile and chromophile pituitary adenoma. Cushing[17] found rapid increase in weight with amenorrhoea in 60 per cent of females with chromophile adenoma before pressure on the optic chiasm became apparent. However, obesity of hypothalamic origin is equally well known ever since O. Marburg[18] described the first incident in a case of internal hydrocephalus (1907).

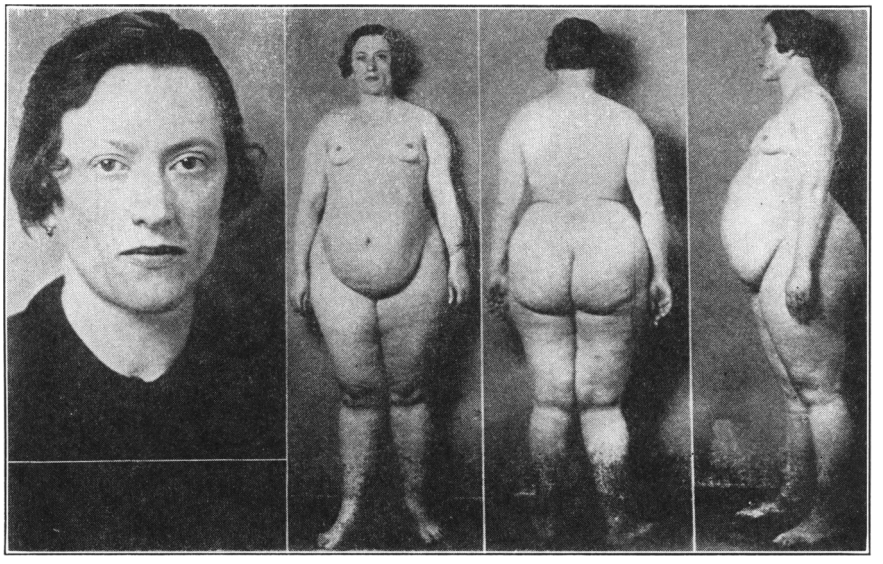

FIG. 3—Lipodystrophia.

Smith has demonstrated in experiments that hypothalamic damage produces obesity without gonadal changes. Pituitary and hypothalamic obesity have identical features and are characterized by the deposition of fat on the trunk, the lower part of the abdomen and the proximal parts of the limbs, whereas the forearms and the calves remain slender. In a few cases the distribution of the fat takes a different form and may result in the so-called lipodystrophia with masses of fat below the girdle and emaciation of the upper parts, particularly the face, where every trace of fat may disappear. We also have seen a case with an accumulation of fat on the neck and abdomen and complete fat atrophy on the extremities.

The pituitary-hypothalamic complex causes obesity not by the failure of a hormone responsible for the catabolism of fat—it is even doubtful whether such a "fat hormone" exists—but by its influence on the fat cells themselves. The combination of obesity or lipomatosis with fat atrophy in definite areas indicates the general neuro-endocrine influence, which renders the fat tissue lipophilic, attracting fat, as well as lipophobic, barring fat, accentuating thus in the females the fat distribution characteristic of the female sex and feminizing the external appearance of males. This is most conspicuous in those instances in which the dis-

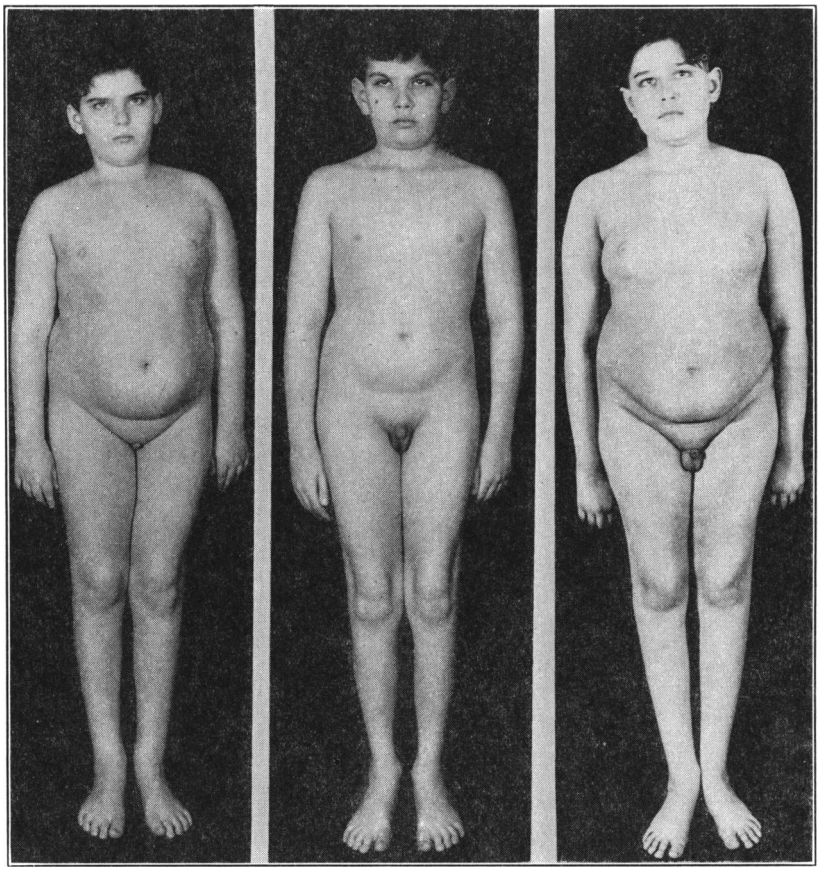

Fig. 4—Three cases of Froehlich's syndrome.

tribution of fat is altered without apparent obesity and fat accumulates above the hipbones, as in the case of a boy with infantile gigantism.

Differentiation between the pituitary and the hypothalamic origin of obesity combined with hyposexualism—if it can be said to be an actual difference at all—depends upon variations in growth. When the pituitary influence predominates, retardation of growth and pituitary dwarfism may result. When the hypothalamic influence is prevalent, growth continues and, owing to the relationship between sex maturation on the one hand and ossification and closure of the epiphyses on the other, leads to the tall eunuchoid type or infantile gigantism.

Children and adolescents with the Froehlich syndrome look very

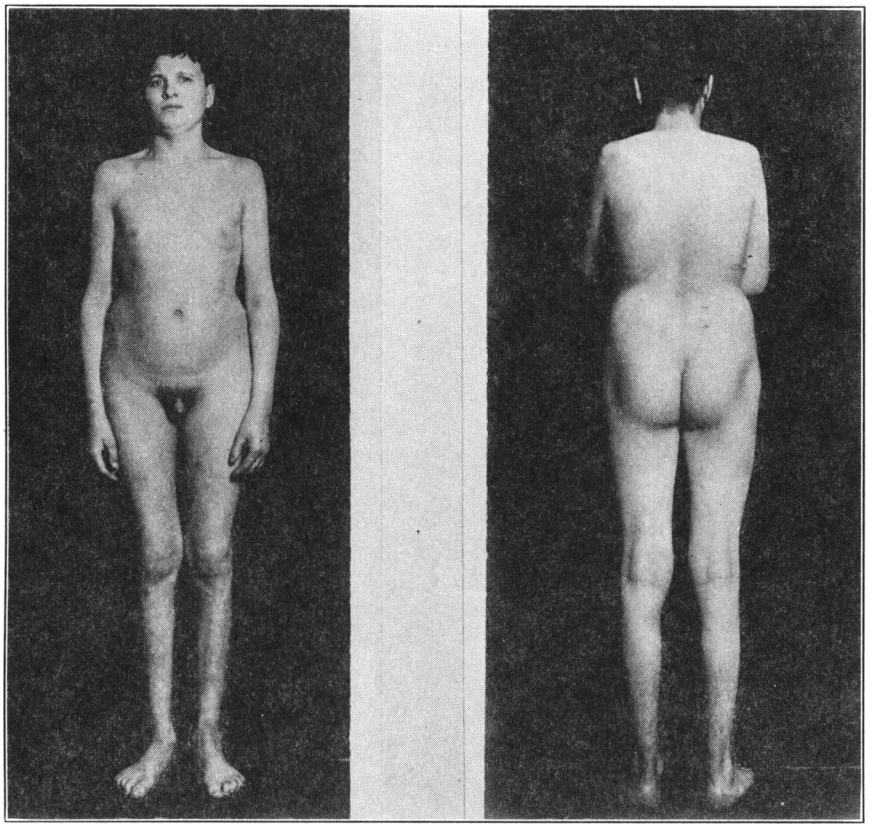

Fig. 5—Infantile gigantism.

much alike, as if belonging to the same family tree, and also have marked similarities in character, temperament and behavior. They retain the infantile habitus over long and are slow in developing a definite individuality. Girls not infrequently develop an inferiority complex and a rather violent desire to normalize their appearance.

This, however, is rather difficult to accomplish. The basic part of the obesity scarcely responds to such dietary restrictions, as are suitable and applicable during the growing stage, when used over a longer period of time. However, not infrequently reduction of weight takes place spontaneously with the onset of sexual maturation. The additional adiposity resulting from overeating can be removed. Overeating in this type is not so much due to a blamable overindulgence as to episodes of hypoglycemia with its feeling of stomach emptiness, acute hunger,

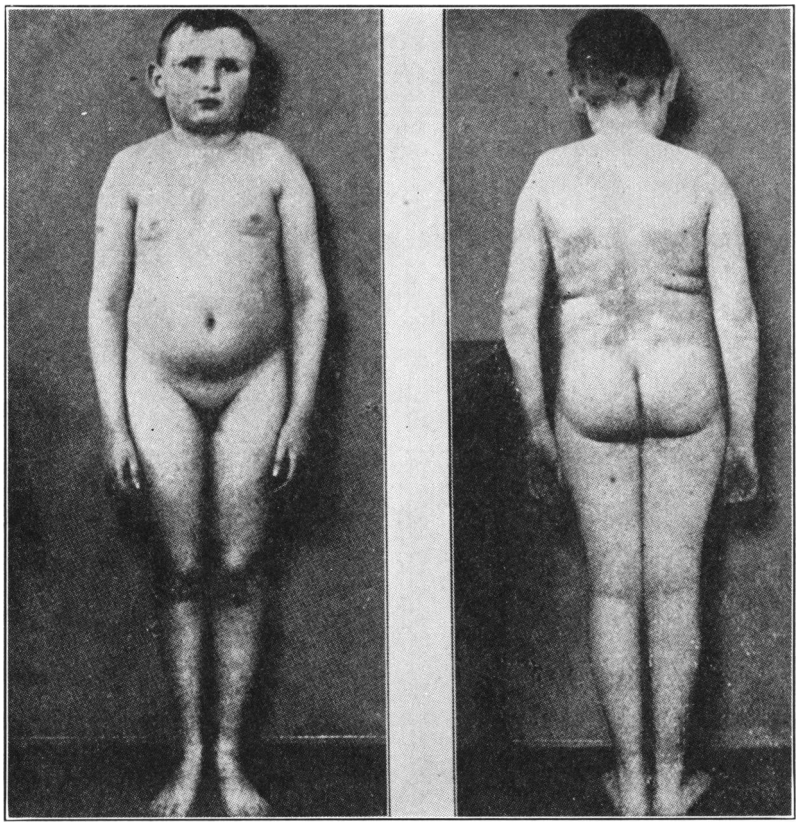

Fig. 6—Pituitary dwarfism.

weakness, craving for food, especially sweets. In such cases the dietary management of the hypoglycemia should be resorted to. During the period of growth, as a rule, a diet almost sufficient in caloric value, rich in proteins and otherwise consisting of fruits, vegetables, particularly in a raw state, with a limited amount of bread and cereals and very poor in fat, is advisable. The administration of thyroid extract is frequently indicated and a dose just below the individual tolerance should be given. Gonadotropic hormone is expedient in order to stimulate the sexual development. This therapy has been successful in a number of cases but is by no means always a panacea. In the fortunate individuals the descent and growth of the testicles can be induced. In the majority of cases sexual maturation sets in spontaneously during the age of adolescence. Thus it occurs that a man with the history and some earmarks of the

Froehlich syndrome may have a son of the same type.

It may be worthwhile mentioning that children with Froehlich syndrome apparently are particularly susceptible to infectious diseases and often are stricken with rheumatic fever. This may be interpreted from the viewpoint that these individuals are more infantile than normal children and thus more susceptible to the infectious diseases of childhood. Or it may point to the relationship of the pituitary-hypothalamic apparatus to the mechanism of defense and immunization.

In conclusion I might emphasize that the relationship between the nervous system and the endocrinal glands, culminating in the hypothalamic-pituitary complex, represents a central point from which the many parts of the medical science are visible; some of them at close range, others still in the far distance, but all of them recognizable as integral parts of the indivisible entity, Medicine.

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